ROLE OF EXTRAHYPOTHALAMIC CORTICOTROPIN-RELEASING FACTOR (CRF) IN DRUG AND ALCOHOL WITHDRAWAL SYNDROMES, F. Weiss, Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA

CRF-containing neurons and CRF receptors in the central nucleus of the amygdala (CeA) are thought to have an important role in the mediation of behavioral and emotional responses to stress. For example, autonomic activation and anxiogenic responses associated with CRF administration can be mimicked by electrical stimulation of the CeA, whereas lesions of this nucleus or local administration of the CRF antagonist α-helical CRF(9-41) effectively reverse the anxiogenic behavioral actions of exogenous CRF. Symptoms of anxiety and negative affect are an integral part of drug and alcohol withdrawal syndromes. It is possible, therefore, that these withdrawal-associated symptoms are mediated by CRF neuronal mechanisms in the CeA. This hypothesis was explored by monitoring the release of CRF in the CeA of rats during ethanol, cocaine, cannabinoid, and opiate withdrawal, and by testing the effects of local administration of α-helical CRF(9-41) on behavioral signs of withdrawal. Removal of chronic ethanol treatment resulted in a progressive elevation of extracellular levels of CRF over a 12 h withdrawal period. Concomitant anxiogenic effects of ethanol withdrawal as measured on the elevated plus maze were effectively reversed by α-helical CRF(9-41). Increased CRF efflux in the CeA was also observed during cocaine withdrawal after 12 hrs of unlimited access to the drug. In addition, a gradual increase in CRF release was apparent already prior to withdrawal during the final hours of the 12 h self-administration episode, suggesting that the neuropeptide may play a role in the aversive subjective effects and/or the decrements in the reinforcing efficacy of cocaine associated with sustained continuous use (cocaine "bingeing"). Withdrawal from chronic cannabinoid treatment precipitated by a cannabinoid receptor antagonist strongly elevated extracellular CRF levels in the CeA with a time course that paralleled closely the behavioral manifestations of the cannabinoid abstinence syndrome. Finally, intra-CeA injections of α-helical CRF(9-41) reversed conditioned place aversion in morphine-dependent rats induced by administration of the opiate antagonist methylnaloxonium into the same site. Together, these findings provide support for an involvement of CRF mechanisms in the CeA in the regulation of behavioral and emotional consequences of drug and alcohol withdrawal and, consequently, in the motivational effects of withdrawal states. (Supported by NIDA DA08426 and NIAAA AA06420).